and insert the following therefor as a separate page after the claims:

-Abstract of the Disclosure

Compounds are disclosed having the general formula R_1 -X- R_2 , wherein R_1 and R_2 are biologically active groups, at least one of which is polypeptidic. X is a non-peptidic polymeric group. R_1 and R_2 may be the same or different. Preferred R_1 and R_2 groups are TNF inhibitors.

In the Claims

Please delete claims 1-14 and 16-44, without prejudice or disclaimer.

Please amend claim 15, as follows:

15. A [substantially purified] compound of the formula R₁-X-R₂, wherein:

[X comprises a non-peptidic polymer having a first reactive group and a second reactive group, wherein said first reactive group is a Michael acceptor; and]

R₁ and R₂ are each a tumor necrosis factor (TNF) inhibitor polypeptide selected from:

(a) 30 kDa TNF inhibitor or 40 kDa TNF inhibitor,

(b) 30 kDa TNF inhibitor or 40 kDa TNF inhibitor, modified to contain at least one non-native cysteine residue, and

(c) a biologically active portion of (a) or (b), wherein R_1 and R_2 bind to TNF; and [comprises a biologically-active molecule having a reactive thiol moiety, said biologically-active molecule is covalently bonded to said non-peptidic polymer by reaction of said thiol moiety with said Michael acceptor, and said biologically-active molecule retains its biological activity after said reaction; and

R₂ comprises a biologically-active molecule or a nonbiologically-active group bonded to said non-peptidic polymer by reaction/with said second reactive group]

X is a non-peptidic polymer having two activated groups linked thereto, said non-peptidic polymer being selected from polyethylene glycol, polypropylene glycol, polyoxyethylated glycerol and other polyoxyethylated polyols, polyvinyl alcohol and other polyalkylene oxides, polyoxyethylated sorbitol or polyoxyethylated glucose.

Please add the following new claims:

73 45

The compound of claim 15, wherein R_1 and R_2 are identical.

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The compound of claim 1, wherein R ₁ and R ₂ are different. The compound of claim 1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor. The compound of claim 2, wherein said 30 kDa TNF inhibitor is modified to contain at least one non-native cysteine residue. The compound of claim 3, wherein said non-native cysteine residue is found at an amino acid residue site selected from the group consisting of 1, 14, 105, 111 and 165. The compound of claim 1, wherein R ₁ and R ₂ are each a portion of said 30 kDa TNF inhibitor. The compound of claim 1, wherein R ₁ and R ₂ are covalently bonded to X by thio-ether bonds. The compound of claim 2, wherein cysteine residues of R ₁ and R ₂ are part of said thio-ether bonds. The compound of claim 3, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. A pharmaceutical composition comprised of an effective amount of the compound of claim 3, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 3, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion thereof, modified to contain a non-native cysteine residue. The compound of claim 2, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	
The compound of claim 1, wherein said 30 kDa TNF inhibitor is modified to contain at least one non-native cysteine residue. The compound of claim 1, wherein said non-native cysteine residue is found at an amino acid residue site selected from the group consisting of 1, 14, 105, 111 and 165. The compound of claim 1, wherein R ₁ and R ₂ are each a portion of said 30 kDa TNF inhibitor. The compound of claim 1, wherein R ₁ and R ₂ are covalently bonded to X by thio-ether bonds. The compound of claim 1, wherein cysteine residues of R ₁ and R ₂ are part of said thio-ether bonds. The compound of claim 1, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. A pharmaceutical composition comprised of an effective amount of the compound of claim 1, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 2, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 2, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	The compound of claim-15, wherein R ₁ and R ₂ are different.
least one non-native cysteine residue. 1. The compound of claim 1. wherein said non-native cysteine residue is found at an amino acid residue site selected from the group consisting of 1, 14, 105, 111 and 165. 2. The compound of claim 1. wherein R ₁ and R ₂ are each a portion of said 30 kDa TNF inhibitor. 2. The compound of claim 1. wherein R ₁ and R ₂ are covalently bonded to X by thio-ether bonds. 3. The compound of claim 1. wherein cysteine residues of R ₁ and R ₂ are part of said thio-ether bonds. 4. The compound of claim 1. wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. 3. A pharmaceutical composition comprised of an effective amount of the compound of claim 1. which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 3. The compound of claim 3. which has been prepared by a method comprising thio-ether bonds when reacted with cysteine residue. 3. The compound of claim 3. which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 3. The compound of claim 1. Which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 3. The compound of claim 1. Which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound of claim 1. Which has been prepared by a method comprising reacting R ₁ with X to form a com	47. The compound of claim 18, wherein R_1 and R_2 are said 30 kDa TNF inhibitor.
The compound of claim 18, wherein said non-native cysteine residue is found at an amino acid residue site selected from the group consisting of 1, 14, 105, 111 and 165. The compound of claim 18, wherein R1 and R2 are each a portion of said 30 kDa TNF inhibitor. The compound of claim 18, wherein R1 and R2 are covalently bonded to X by thio-ether bonds. The compound of claim 18, wherein cysteine residues of R1 and R2 are part of said thio-ether bonds. The compound of claim 18, wherein R1 and R2 are attached to said polyethylene glycol via a cysteine residue. A pharmaceutical composition comprised of an effective amount of the compound of claim 18 in a pharmacologically acceptable carrier. The compound of claim 18, which has been prepared by a method comprising simultaneously reacting R1 and R2 with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 18, which has been prepared by a method comprising reacting R1 and R2 are said 30 kDa TNF inhibitor or a portion thereof, modified to contain a non-native cysteine residue. The compound of claim 18, which has been prepared by a method comprising reacting R1 with X to form a complex R1-X and subsequently reacting said complex R1-X with R2 to form the compound R1-X-R2, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 18, which has been prepared by a method comprising reacting R1 with X to form a complex R1-X and subsequently reacting said complex R1-X with R2 to form the compound R1-X-R2, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	
acid residue site selected from the group consisting of 1, 14, 105, 111 and 165. The compound of claim 12, wherein R ₁ and R ₂ are each a portion of said 30 kDa TNF inhibitor. The compound of claim 12, wherein R ₁ and R ₂ are covalently bonded to X by thio-ether bonds. The compound of claim 13, wherein cysteine residues of R ₁ and R ₂ are part of said thio-ether bonds. The compound of claim 13, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. A pharmaceutical composition comprised of an effective amount of the compound of claim 13, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 13, which has been prepared by a method comprising reacting R ₁ and R ₂ with X; wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine residue. The compound of claim 13, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 14, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	reast one non-native cysteme residue.
inhibitor. M. The compound of claim 15, wherein R ₁ and R ₂ are covalently bonded to X by thio-ether bonds. 2. The compound of claim 57, wherein cysteine residues of R ₁ and R ₂ are part of said thioether bonds. D. The compound of claim 16, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. J. A pharmaceutical composition comprised of an effective amount of the compound of claim 16 in a pharmacologically acceptable carrier. J. The compound of claim 17, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. J. The compound of claim 18, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion thereof, modified to contain a non-native cysteine residue. J. The compound of claim 18, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. J. The compound of claim 37, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	
bonds. 7. The compound of claim \$1, wherein cysteine residues of R ₁ and R ₂ are part of said thioether bonds. 7. The compound of claim \$1, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. 7. A pharmaceutical composition comprised of an effective amount of the compound of claim \$1, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 7. The compound of claim \$1, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine residue. 7. The compound of claim \$1, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 7. The compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound the compound of claim \$1, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound the compound the compound the compound the compound the compound the comp	
2. The compound of claim 12, wherein cysteine residues of R ₁ and R ₂ are part of said thioether bonds. 2. The compound of claim 12, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. 3. A pharmaceutical composition comprised of an effective amount of the compound of claim 13 in a pharmacologically acceptable carrier. 3. The compound of claim 14, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 3. The compound of claim 13, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion thereof, modified to contain a non-native cysteine residue. 3. The compound of claim 13, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 3. The compound of claim 3, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	·
ether bonds. D 3. The compound of claim 12, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. A pharmaceutical composition comprised of an effective amount of the compound of claim 12 in a pharmacologically acceptable carrier. 3. The compound of claim 13, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 3. The compound of claim 13, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 3. The compound of claim 3, wherein X ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	bolids.
The compound of claim 18, wherein R ₁ and R ₂ are attached to said polyethylene glycol via a cysteine residue. A pharmaceutical composition comprised of an effective amount of the compound of claim is in a pharmacologically acceptable carrier. The compound of claim 18, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 18, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound of claim 18, which has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 18, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues.	-
In a pharmacologically acceptable carrier. The compound of claim 18, which has been prepared by a method comprising simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 58, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion thereof, modified to contain a non-native cysteine residue. The compound of claim 18, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 18, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion	/ δ / δ . The compound of claim $1/\delta$, wherein R_1 and R_2 are attached to said polyethylene glycol via
simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 58, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion thereof, modified to contain a non-native cysteine residue. The compound of claim 18, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim 18, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion	· ·
thereof, modified to contain a non-native cysteine residue. 57. The compound of claim 18, which has been prepared by a method comprising reacting R ₁ with X to form a complex R ₁ -X and subsequently reacting said complex R ₁ -X with R ₂ to form the compound R ₁ -X-R ₂ , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. 58. The compound of claim 18, wherein R ₁ and R ₂ are said 30 kDa TNF inhibitor or a portion	simultaneously reacting R ₁ and R ₂ with X, wherein X has at least two reactive groups capable of
with X to form a complex R_1 -X and subsequently reacting said complex R_1 -X with R_2 to form the compound R_1 -X- R_2 , wherein X has at least two reactive groups capable of forming thio-ether bonds when reacted with cysteine amino acid residues. The compound of claim $\frac{1}{2}$, wherein R_1 and R_2 are said 30 kDa TNF inhibitor or a portion	
	with X to form a complex R_1 -X and subsequently reacting said complex R_1 -X with R_2 to form the compound R_1 -X- R_2 , wherein X has at least two reactive groups capable of forming thio-ethe bonds when reacted with cysteine amino acid residues.

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